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ORIGINAL ARTICLE

Shall we diagnose metabolic syndrome in adolescents?

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Abstract

BACKGROUND: The clinical value of the diagnosis of metabolic syndrome (MS) in children and adolescents remains unclear. The aim of the present study was to assess the occurrence of metabolic complications, other than included in 2007 IDF MS definition, in obese children and adolescents

METHODS: The study included 75 (33 boys) obese adolescents (mean age 13.9 years, mean BMI SDS 4.49). Classical (fasting glucose, TGL, HDL, blood pressure) and non classical (insulin resistance [HOMA-IR], creatinine, AST, ALT, uric acid, fibrinogen, liver US and 24h BP profile) risk factors were compared between groups with and without MS. 15(8 boys) met the 2007 IDF criteria for MS.

RESULTS: Patients with MS presented with significantly lower: BMI SDS (4.2 vs. 5.8, p=0.02), mean 24h SBP (0.8 vs. 1.0, p=0.03), and uric acid level (352.1 vs. 414.0, p=0.01). In both groups a significant percentage of abnormal results of 24hABPM (up to 42.9 and 57.6%), insulin resistance (85.7 % and 61.1%), non alcoholic fatty liver disease (57.4 % and 38.9 %) and hyperuricemia (69.2 % and 55.3%) was observed.

CONCLUSION: Recognizing the metabolic syndrome in adolescents does not provide any additional clinical benefits. It seems that in every obese child a wide, personalized diagnostic work-up should be performed.

Abbreaviations:

ABPM	- ambulatory blood pressure monitoring,
ALT	- alanine aminotransferase,
AST	- asparagines minotransferase,
BMI	- body mass index,
DBP	- diastolic blood pressure,
dDBP	- mean day-time diastolic blood pressure,
dSBP	- mean day-time systolic blood pressure,
dMAP	- mean day-time arterial pressure,
eGFR	- estimated glomerular filtration rate,
HDL	- high density cholesterol,
IDF	- International Diabetes Federation,
MS	- metabolic syndrome,
MAP	- mean arterial pressure,
NAFLD	- non alcoholic fatty liver disease,
nDBP	- mean night-time diastolic blood pressure,
nSBP	- mean night-time systolic blood pressure,
nMAP	- mean night-time arterial pressure,
TGL	- triglycerides,
SBP	- systolic blood pressure,
SDS	- standard deviation score

INTRODUCTION

The growing prevalence of obesity in children and adolescents has highlighted a need for the identification of young individuals at particular risk of metabolic complications. For this purpose many attempts have been made to create definition of metabolic syndrome (MS) suitable for youths. Unfortunately proposed criteria have been mainly based on already existing definitions for adults adjusted for pediatric use (Zimmet *et al.* 2007; Cook *et al.* 2003; Jolliffe&Janssen 2007; Pacifico *et al.* 2011; Tailor *et al.* 2010). Because the studies with hard clinical endpoints, such as morbidity and mortality, are still lacking, currently used cutoffs vary widely between definitions, and different definitions do not classify the same adolescents as having MS (Kelly *et al.* 2011; Vanlancker *et al.* 2017). Moreover, the MS definitions include only selected biochemical parameters, that practically reflect only advanced, already existing, metabolic complications in adults. Such limitation of evaluated parameters does not include early markers of cardiovascular disorders, and therefore don't allow the identification of young patients at risk of metabolic complications (Kelly *et al.* 2011; Vanlancker *et al.* 2017). Some authors point to the crucial role of many other than traditional MS parameters in the early recognition of metabolic disturbances and prevention of complications in obese adolescents. Abnormal circadian blood pressure rhythm, impaired glucose tolerance, hyperuricemia and hyperfibrinogenemia, non alcoholic fatty liver disease seem to be not less important than abnormal results of ambulatory measurements of blood pressure, elevated triglycerides, low HDL cholesterol nor elevated fasting glucose (Strojny *et al.* 2017; Mosca *et al.* 2017; Lovely *et al.* 2013). Therefore to date, there is no clear consensus about the clinical value of the recognition of MS in children and adolescents on the basis of classical definitions (Vanlancker *et al.* 2017).

The aim of the study was to assess the occurrence of metabolic complications, other than included in 2007 IDF MS definition, in obese children and adolescents.

MATERIAL

The study included 75 patients (33 boys), at the age of puberty (mean 13.9 years) with simple obesity (mean BMI SDS 4.49) (Table 1). The patients were recruited among patients referred for consultation to the Endocrine Department Outpatient Clinic in Children's University Hospital in Krakow.

The aim of the study was to assess the occurrence of metabolic complications, other than included in 2007 IDF MS definition, in obese children and adolescents.

METHODS

Body weight and height were measured to the nearest 0.1 kg, and 0.1 cm using a stadiometer (Harpenden) and a balanced scale (Seca). Waist circumference was obtained at the midpoint between the lowest rib and the iliac. As the reference to calculate SDS for waist and hip circumference, normal values for the local population were used. 24-hour BP monitoring was performed using an Ambulatory BP Monitor (Space labs 90217, USA), with a cuff which was the same size as the one used to measure casual blood pressure. Recordings with at least 70% valid readings and at least one reading every hour were considered for the analysis. The following parameters were analyzed: mean 24-h systolic (SBP), diastolic (DBP), and mean arterial pressure (MAP), mean day-time systolic (dSBP), diastolic (dDBP), and MAP (dMAP), mean night-time systolic (nSBP), diastolic (nDBP), and MAP (nMAP). Blood pressure load was calculated separately for the awake and asleep periods. BP load was defined as the percentage of valid BP measurements above a set threshold (95^{th} percentile for sex and the height) value (Urbina *et al.* 2008; National High Blood Pressure Education Program Working Group 2004). Loads in excess of 30% were considered elevated. Loads in excess of 50% were considered severely elevated. The calculation of nocturnal dipping was based on a formula by the American Heart Association: [(dSBP– nSBP)/dSBP] × 100. Normal dipping was defined as a ≥10% decline in BP (Urbina *et al.* 2008; National High Blood Pressure Education Program Working Group 2004). Standard oral glucose tolerance tests were performed with the assessment of fasting and postload glucose and insulin levels. HOMA-IR was calculated using the formula: [fasting insulin level (μIU/mL) x fasting glucose level (mmol/L)]/22. The definition of insulin resistance was based on a HOMA-IR threshold set for adolescents (> 3.16) (Keskin *et al.* 2005). Uric acid (UA), aspargine aminotransferase (AST), alanine aminotransferase (ALT), glucose, triglycerides (TGL), high-density lipoprotein cholesterol (HDL) and creatinine concentrations were estimated in the fasting blood sample by the dry chemistry method with a Vitros 5.1.FF machine (Ortho-Clinical Diagnostics, Rochester, NY, USA). Estimated glomerular filtration rate (eGFR) was calculated by on-line calculator based on Schwartz and Counahan-Barratt Methods adjusted for pediatric population (http://nephron.com/bedside_peds_nic.cgi).

Ultrasonography was performed using Philips EnVisor unit with an 3.5 MHz scanhead. Non alcoholic fatty liver disease was defined by the presence of surrogate markers: ALT levels (>35 IU/L) and increased echogenicity of the liver on ultrasound examination (Vajro *et al.* 2012).

STATISTICS

Categorical variables were expressed as counts and percentages. Empirical distribution of continuous variables was described using mean, standard deviation (notation used: mean [SD]). Statistical significance of differences between two independent groups was assessed using the Mann-Whitney test or chi-square test as appropriate. A p-value less than 0.05 was considered an indication of a statistically significant result. All statistical analyses were performed using Statistica 12 software (StatSoft Poland).

RESULTS

Among the study group only 15 (8 boys) met the 2007 IDF criteria for MS. Surprisingly, they presented with significantly higher mean HDL level, lower TGL level, and lower mean DBP (Table 2). Patients that met criteria for MS presented with significantly lower: BMI SDS, mean 24h SBP, and uric acid level. Patients in both groups (with MS, and who did not meet MS criteria) presented a significant percentage of abnormal results of 24h ABPM (up to 42.9 and 57.6%), and results of biochemical analysis. Insulin resistance assessed on the basis of HOMA-IR calculation with the cut-off value recommended for pubertal age was confirmed in 85.7% patients with MS and 61.1 without MS. NAFLD and elevated UA were present in 57.4% and 69.2% of patients with MS respectively, and in 38.9% and 55.3% of non-MS participants. There were no significant differences regarding frequency of that disorders in both groups (Table 3.).

Tables 1, 2 and 3 show the complete results of the present study.

Tab. 1. Comparison of the selected, "non classical" parameters in patients with and without MS.

Parameter	Metabolic syndrome	Non metabolic syndrome	p-value
Age [years]	12.8 (2.47)	14.3 (2.19)	0.02*
BMI SDS	4.2 (1.41)	5.8 (2.86)	0.02*
24h SBP [SDS]	1.2 (0.99)	1.9 (1.08)	0.03*
24h DBP [SDS]	0.8 (0.72)	1.0 (0.62)	0.15
Night dip [%]	9.5 (5.29)	10.3 (5.96)	0.57
eGFR	114.6 (17.83)	109.3 (16.67)	0.38
Glucose 120' post load [mmol/L]	5.9 (2.11)	6.3 (1.40)	0.11
Insulin 0' (fasting) [µIU/mL]	20.9 (10.80)	24.6 (10.17)	0.11
Insulin 120' post load [µIU/mL]	109.7 (61.14)	130.7 (53.52)	0.16
HOMAIR	4.2 (2.26)	4.9 (2.24)	0.11
AST [IU/L]	28.5 (8.58)	31.5 (13.19)	0.46
ALT [IU/L]	35.5 (17.69)	46.9 (35.49)	0.16
GGT [IU/L]	40.7 (38.72)	30.1 (23.71)	0.10
Uric acid [µmol/L]	352.1 (66.17)	414.0 (86.18)	0.01*
Fibrinogen [g/L]	3.8 (0.63)	3.6 (0.65)	0.39
Total cholesterol	4.4 (0.87)	4.7 (0.75)	0.19
LDL cholesterol	2.7 (0.78)	3.0 (0.82)	0.10

Notation used: mean (SD), *statistically significant values (p<0,05)

DISCUSSION

The problem of obesity and its complications in children and adolescents in 21st century is undoubted. The ongoing questions remain about how to diagnose these complications at the earliest possible stage, and what should be the best moment for therapeutic intervention.

There is no doubt, that metabolic consequences of obesity are not only a problem of adulthood. In fact, risk factors of cardiovascular disease and type 2 diabetes are already present in children and adolescents (Cook *et al.* 2009). In early 2000s, it appeared that creating a definition of the MS for children and adolescents would identify individuals at the highest risk of developing complications, similarly to the adult population (Zimmet *et al.* 2007; Cook *et al.* 2003; Jolliffe&Janssen 2007; Pacifico *et al.* 2011; Tailor *et al.* 2010). Metabolic syndrome has been defined as the clustering of risk factors for cardiovascular disease and type 2 diabetes mellitus, such as obesity, dyslipidemia, hypertension, and glucose intolerance. Creating the right definition, however, has been more difficult than expected. It seems,

Tab. 2. Comparison of the classical parameters of the metabolic syndrome in patients with and without diagnosis of MS based on the 2007 IDF definition.

Parameter	Metabolic syndrome	Non metabolic syndrome	p-value
Fasting glucose [mmol/L]	4.5 (0.37)	4.5 (0.32)	0.91
HDL [mmol/L]	1.17 (0.19)	0.8 (0.15)	<0.001*
TGL [mmol/L]	1.3 (0.42)	2.5 (1.70)	<0.001*
SBP [SDS]	1.2 (0.90)	0.8 (1.00)	0.03*
DBP [SDS]	0.8 (0.71)	1.0 (0.60)	0.02*

Notation used: mean (SD), *statistically significant values (p<0.05)

Tab. 3. Comparison of the selected, "classical" parameters in patients with and without MS.

	Metabolic syndrome [%]	Non metabolic syndrome [%]	χ2 Pearsons	p-value
24h MAP> 2 SDS	0	5.1	0.7	0.4
24h SBP load >30%	21.4	30.5	0.5	0.5
24h SBP load >50%	7.1	11.9	0.3	0.6
24h DBP load >30%	14.3	11.9	0.06	0.8
24h DBP load >50%	0	1.7	0.2	0.6
Night dip <10%	42.9	57.6	0.99	0.3
Low eGFR	7.1	3.4	0.4	0.5
HOMAIR >3.16	85.7	61.1	3.06	0.08
Hiperurycaemia	69.2	55.4	0.8	0.4
Non alcoholic fatty liver disease	57.4	38.9	1.5	0.2

that the underlying mechanisms leading to the development of metabolic complications of obesity in adolescence are different than in adults. However it is clear, that the cardinal feature is insulin resistance, there is a lack of clarity as to how insulin resistance in childhood is best assessed, in what clinical disorders it occurs, and whether it can be treated or prevented (Keskin *et al.* 2005; Reaven 2013; Levy-Marchal *et al.* 2010). A factor that significantly impedes interpretation of the results of the research is that growth and puberty interfere with the variables used to define MS (Keskin *et al.* 2005; Brambilla *et al.* 2007). Therefore the cutoff values are difficult to set up. Due to the lack of the studies with hard clinical endpoints in this field, cutoffs vary widely between definitions, and different definitions do not classify the same adolescents as having MS. As a consequence the prevalence of MS in adolescents varies a lot between studies. In a review, the prevalence in the general population of adolescents ranged from 2.0 to 9.5% in USA and from 1.4 to 4.1% in Europe (using the IDF, WHO, and NCEP-ATP definition) (Tailor *et al.* 2010). The results of the present study show, that current definition of MS is not useful for the identification of the pediatric patients at the highest risk of cardiovascular or metabolic risk. Despite only 20% of participants met criteria of MS, most of them presented abnormal results of assessed parameters. Interestingly, even classical parameters, such as the mean values of TGL and HDL were significantly less favorable in patients without diagnosis of MS. The question remains whether it is actually valuable to diagnose MS in children and adolescents to start early with interventions ? The answer seems to be: no. Nevertheless the underlying mechanisms leading to these anthropometric, physiological, and biochemical abnormalities are incompletely understood. However it is clear, that the cardinal feature is insulin resistance, there is a lack of clarity as to how insulin resistance in childhood is best assessed, in what clinical disorders it occurs, and whether it can be treated or prevented (Reaven 2013; Levy-Marchal *et al.* 2010). The situation is even more complicated by recently published studies, that point to higher plasticity of cardiovascular system in the developmental period, in comparison to adults (Hochberg 2011; Tain & Joles 2015). This phenomenon is known as Developmental Plasticity or Programming since the genetic program adapts to existing environmental conditions resulting in different phenotypes (Hochberg 2011). Therefore patients with prehypertension and insulin resistance have an increased risk of complete hypertension, type 2 diabetes and cardiovascular morbidity and mortality. On the other hand, early intervention, at the pre-clinical phase, can significantly improve prognosis. Hence, early detection of individuals that are at metabolic complications and early inter-

vention to reprogram metabolic complications may well allow us to reduce the future burden of childhood obesity (Starzyk *et al.* 2009).

CONCLUSION

Recognizing the metabolic syndrome in children and adolescents does not provide any additional clinical benefits. It seems that in every child with obesity a wide, personalized diagnostic work-up should be performed, to allow intervention at the stage of preclinical changes.

ETHICS

The investigation was conducted according to the principles expressed in the Declaration of Helsinki. The study has been approved by Jagiellonian University Bioethical Committee (decision number KBET/38/B/2008); all participants and their parents signed informed consent.

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AUTHORS DISCLOSURE STATEMENT

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